Regulatory Toxicology and Pharmacology xxx (2015) 1–12

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market

Diana Brito da Justa Neves [a], Eloisa Dutra Caldas [b, *]

[a] National Institute of Criminalistics, Federal Police Department, 70610-200 Brasilia, DF, Brazil
[b] Laboratory of Toxicology, Faculty of Health Sciences, University of Brasília, 70910-900 Brasilia, DF, Brazil

ARTICLE INFO

Article history:
Received 12 January 2015
Received in revised form
16 June 2015
Accepted 17 June 2015
Available online xxx

Keywords:
Dietary supplements
Legislation
Irregular products
Adulteration
Hormones
Fat-burners
Brazil
European Union
United States

ABSTRACT

The objectives of this work were to evaluate current legislation on dietary supplements in the United States, the European Union and Brazil, and the profile of adulterated and/or irregular products on these markets. Due to a less restrictive legal framework, a supplement product that is freely available in the US may be considered a drug or even be proscribed in the EU and Brazil, thus giving rise to a clandestine market based on smuggling. From 2007 to 2014, the United States Food and Drug Administration reported 572 cases of supplement adulterations in the country, mainly products for sexual enhancement (41.6%). Data from the European Union Rapid Alert System for Food and Feed showed 929 adulterations during the same period, over 40% due to unauthorized ingredients or undeclared medicines. From 2007 to 2013, the Brazilian Federal Police Department seized 5470 supplement products, 92.2% with an American-declared origin. Qualitative chemical analyses performed on 2898 products found 180 adulterations, 41.1% due to undeclared drugs, mainly anabolic steroids, anorectics and products for erectile dysfunction, all considered medicines in Brazil. Educating the public regarding the potential risks they are taking when consuming adulterated or irregular products is necessary to protect the health of consumers.

1. Introduction

Dietary, food or nutrient supplements, referred to in this work as supplements, may be defined as concentrated sources of nutrients or other substances with a nutritional or physiological effect, marketed in dose form, with the purpose of supplementing the normal diet (EC, 2002). The use of supplements has been increasing worldwide in the last decades, even though the efficacy and safety of some of these products are still under discussion in the scientific community (Petroczi et al., 2011; Eudy et al., 2013; Cohen, 2012; Sepkowitz, 2013; Lachenmeier et al., 2013; Finley et al., 2014).

Most studies addressing the consumption of supplements worldwide involve athletes or physically active people, who are the main consumers of these products. Consumption rates for these populations in Brazil range from 20 to 94%, with an increase in recent years (De Rose et al., 2006; Goston and Correia, 2010; Silva and Marins, 2013; Carvalho-Silva et al., 2012; Fayh et al., 2013; Nogueira et al., 2013). Similar results were reported in Spain (28%; Oliver et al., 2011), Iran (66.7%; Saeedi et al., 2013), Germany (91.1%; Diehl et al., 2012), Canada (98.6%; Kristiansen et al., 2005), and the USA (46.7%; Jacobson et al., 2012).

The legal framework for supplements varies among countries. In Brazil, the category "dietary supplement" does not exist, and these products are placed in other food categories such as food for athletes, vitamins and/or mineral supplements, and foodstuffs with functional properties or health claims (SVS, 1998; ANVISA, 1999a,b; ANVISA, 2010a,b,c). Substances with therapeutic functions cannot be included in these products, as they are classified as medicines and are specifically regulated (Brazil, 1976). The distinction between foodstuffs and medicinal products is also clear in the European Union, (EC, 2001), although there are the so-called "borderline products", which contain substances that may have pharmacological effects at a given dose (Lachenmeier et al., 2012). In the United States, legislation allows a wider range of products to be marketed as supplements, which may contain a substance that has been

* Corresponding author.
E-mail addresses: diana.dbjn@dpf.gov.br (D.B. Justa Neves), eloisa@unb.br (E.D. Caldas).

http://dx.doi.org/10.1016/j.yrtph.2015.06.013
0273-2300/

approved as a new drug, certified as an antibiotic, or licensed for biological use if, prior to such approval, it has been marketed as a supplement or food, unless stated otherwise by specific regulation (USA, 1994). Thus, many products that are legally commercialized in the United States as supplements are considered medicines in Brazil and in Europe and, as such, need to comply with all the obligatory requirements for a medicine product.

In addition to the legal issues, another potential problem related to supplements is the risk of adulteration. Supplements can be adulterated either unintentionally due to cross contamination, or intentionally with drugs to ensure or enhance the product's results. The substances reported to be most frequently used in supplement adulteration are steroids, stimulants, anorectics and phosphodiesterase inhibitors, used for erectile dysfunction (Geyer et al., 2004, 2008; Petroczi et al., 2011; Damiano et al., 2014).

The aims of this work were to overview the legislation related to supplements in Brazil, the European Union and the United States, the international scenario of supplement adulteration, and to evaluate supplements seized and analyzed by the Brazilian Federal Police Department (DPF) from 2007 to 2013.

2. Legal framework for dietary supplements

2.1. United States legislation

The first attempts made by the United States Food and Drug Administration (FDA) to regulate dietary supplements as drugs occurred in the 1960s and 1970s, which met strong resistance from consumers, including protests, and from manufacturers. In 1994, the US Congress approved the Dietary Supplement Health Education Act (DSHEA), which established that dietary supplements be treated as foods (USA, 1994), not drugs, which are regulated more stringently (USA, 1938). This Act effectively assured the public unrestricted access to dietary supplements (Brownie, 2005).

According to the DSHEA, dietary supplements may contain a vitamin, mineral, herb, botanical, amino acid, or a dietary substance to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any of these ingredients. In addition, they may include substances that have been approved as a new drug or certified as an antibiotic if they were, prior to such approval, marketed as a dietary supplement or food (USA, 1994). This means that many substances with pharmacological actions can be regularly sold as food supplements in the US.

Under the DSHEA, supplement manufacturers are not required to notify, gain approval, or register their products with the FDA, nor are they obliged to obtain FDA approval to release the product on the market (USFDA, 2011; Brownie, 2005; USA, 1994). They must comply with specific dietary supplement Good Manufacturing Practices (GMPs), which were established by the FDA in 2007 (USFDA, 2007). These GMPs include quality control procedures and recording requirements for each step in the manufacturing process, to ensure that the final product contains the appropriate ingredients at the right dose, without the presence of contaminants, such as toxins, bacteria, pesticides, glass, and heavy metals, or improper packaging and labeling.

Also according to the DSHEA, the FDA must prove – at its own expense – that a supplement presents an unreasonable risk of illness or injury before acting to remove it from the market as being unsafe. Contrary to what is required for drugs, manufacturers are not legally required to provide evidence that their product is safe or effective. Structure or function claims can be made on the supplement's label as long as the manufacturer has substantiation that such claims are "truthful and not misleading" and declares that "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (USFDA, 2011; Brownie, 2005; USA, 1994). The supplement label can also contain health claims, which must be authorized by the FDA and meet a significant scientific agreement (SSA), based on evidence from well-designed studies and agreement among experts (USFDA, 2009). Additionally, health claims can be used when they are based on authoritative statements from federal scientific bodies, within the FDA Modernization Act (USFDA, 1997), or when there are qualified health claims based on less scientific evidence but approved by the FDA, using standardized qualifying language (USFDA, 2003; Corby-Edwards, 2013).

The only case of necessary notification to the FDA is when manufacturers intend to include a new dietary ingredient in their products, meaning an ingredient that was not marketed as food in the US before October 15, 1994 (USFDA, 2013). In this situation, manufacturers are required to notify the FDA of their plans 75 days before the product goes to market, and to submit evidence that the dietary ingredient would be reasonably expected to be safe under the conditions of use recommended or suggested in the supplement labeling (USFDA, 2013; USFDA, 2013b; USA, 1994). Many manufacturers fail to report their intention to include new dietary ingredients, which has led to the withdrawal of some well-known products from the market (USFDA, 2013).

Only in 2011 did the US government introduce slightly more stringent measures to regulate the supplement market. The Food Safety Modernization Act (FSMA), which went into effect on January 4, 2011, changed part of the Federal Food, Drug and Cosmetic Act (USA, 1938), declaring that an officer or a qualified FDA employee may order the withdraw of any food item if they have reason to believe that it is adulterated or misbranded. If there is a reasonable doubt that consumption of a food item will cause serious adverse health consequences to humans and animals, the Agency may require that its distribution or sale be immediately ceased (USA, 2011; USFDA, 2013b). It was based on this new Act that the FDA managed to take OxyElite Pro off the market, due to the reasonable probability that it was related to several cases of liver failure caused by a new ingredient, aegeline, whose safety for consumers had not been demonstrated (USFDA, 2013b).

2.2. European Union legislation

In the European Union (EU), food is defined as "any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. 'Food' includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment". It is clearly stated in Regulation (EC) 178/2002 that "food" shall not include medicinal products (EC, 2002b). There are also several norms to regulate food products, such as Regulation 1925/2006 (which refers to fortified foods; EC, 2006b), Directive 2002/46/EC (which refers to food supplements, specifically vitamins and minerals; EC, 2002), and Regulation 1924/2006 (which refers to nutrition and health claims; EC, 2006). Some of these norms already foresee the need for establishing additional guidelines to cover a wider range of products already available on the market. The area is deemed well-regulated, although the norms may be difficult to interpret (Petroczi et al., 2011).

Medicinal products are defined as "(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

diagnosis" (EC, 2004). These products may not be placed on the market without a prior authorization issued by the competent authorities of the Member State; requests for such authorization must be accompanied by an evaluation of potential environmental risks posed by the product, adverse reactions and results of pharmaceutical tests, pre-clinical tests and clinical trials, among others (EC, 2001).

In addition to these definitions and the requirement that foods may not contain medicinal products, the European Union also includes the so-called "borderline products", referring to products containing substances that may, or may not, have pharmacological action depending on their dosage (Lachenmeier et al., 2012; Coppens et al., 2006). Such products were marketed as medicines until 1965, when Directive 65/65/EEC (EEC, 1965) stated that quality, efficacy and safety data were required for medicinal products. When these data could not be provided for a borderline product, the manufacturer simply changed its label from "medicine" to "dietary supplement" and continued to market it (Lachenmeier et al., 2012).

In the European Union, it is up to each Member State to decide whether a herbal or botanical product falls within the definition of a medicinal product. Herbs and botanical extracts may be present in functional foods, dietary supplements, and also in medicines, and a product would be considered a medicine when presented as having therapeutic or prophylactic properties, or used for medical diagnoses (EC, 2004; Eussen et al., 2011; Coppens et al., 2006). This may lead to a situation in which a product containing a bioactive ingredient at a certain dosage could be considered a dietary supplement in some Member States, but registered as a medicine in others. It is also possible that in a single Member State a given herb or botanical extract is sold both as a medicine and as a supplement, depending on its dosage and form (Eussen et al., 2011; Coppens et al., 2006).

EU legislation establishes that in cases of doubt regarding the "food × drug" nature of a product, the product should be regarded as a medicine, complying with the jurisprudence that has already been established by the European Court of Justice in borderline cases (EC, 2004; Coppens et al., 2006b).

The criterion of "possessing pharmacological action" is currently seen by EU courts as the most important indication to classify borderline products (Lachenmeier et al., 2012). A partial agreement was reached in 2008, suggesting that food and medical products could be distinguished based on the homeostasis of the body. Products intended to support, maintain or optimize normal physiological processes (without altering or blocking them) would be considered as foods, whereas medicines would be those intended to prevent disease or to correct these physiological processes when they are beyond normality, and therefore pathological (CE, 2008).

An important point is that any pharmacological action depends on the concentration of the substance in the body, and therefore a numerical threshold for each compound should be defined above which pharmacological action can be assumed (Lachenmeier et al., 2012). The Council of Europe (2008) reinforced the importance of evaluating a minimal therapeutic dosage. If a product contains a substance at levels below its minimal therapeutic dosage, it is no longer considered a medicine (CE, 2008; Lachenmeier et al., 2012; Coppens et al., 2006).

2.3. Brazilian legislation

In Brazil, the legal definition of medicine is "a pharmaceutical product, technically obtained or manufactured, with prophylactic, curative or palliative purposes, or destined to diagnose" (BRAZIL, 1973). Foodstuff is defined in Decree-Law 986/1969 as any substance or mixture of substances, in solid, liquid, paste or any other suitable form, aimed at providing the human organism with the normal elements required for its formation, maintenance and development (BRAZIL, 1969). This Decree clearly states that products with medicinal or therapeutic properties, regardless of how they are presented or consumed, cannot be considered as food.

There are many products, however, that are still classified as food according to Brazilian legislation but may nevertheless resemble medicines, either because they were "technically obtained or manufactured", are presented in tablet or capsule form and sold in pharmacies, or because they seem to have therapeutic properties. These products are classified under several categories, all under the jurisdiction of the National Health Surveillance Agency (ANVISA), with each having its specific regulations. Some examples include food products for athletes, vitamins and/or mineral supplements, and foodstuffs with functional properties or health claims. None of these products can contain substances with medicinal or therapeutic properties and, to avoid confusion between "functional properties" or "health claims" and therapeutic purposes, the norms specify what products can be sold under which category and what claims can be made on their labels. A summary of the main categories of food that are similar to dietary supplements, their legal definitions, and regulatory norms are shown in Table 1.

It is important to emphasize that some restrictions that are stated in a specific norm may apply to all other categories of food. For example, Ordinance n° 32/1998 states that vitamin and/or mineral supplements cannot contain more than 100% of the Recommended Daily Intake (RDI) of any vitamin and/or mineral (SVS, 1998). ANVISA Resolution RDC 18/2010 states that food for athletes shall not contain stimulants (with exception of caffeine), hormones, or other substances considered doping by the World Anti-Doping Agency (WADA) or related legislations, nor substances with therapeutic properties, including herbal drugs, or their association with nutrients or non-nutrients (ANVISA, 2010a,b,c). These and other restrictions stated in other sanitary norms are valid for all foods, once they are merely ratifications or exemplifications of what is stated in Decree-Law 986/1969.

Another peculiarity of Brazilian legislation is that herbal products, in general, are not considered food. Some plant extracts/derivatives may be commercialized under the "new foods and new ingredients" category that demands pre-market registration at ANVISA, such as *Plantago ovata* (a fiber supplement). The full list of approved new foods and new ingredients is available at the ANVISA website. Products containing other herb extracts must be registered as phytotherapic medicines, and require safety and efficacy data (ANVISA, 2014a,b,c,d).

An additional relevant aspect is the differentiation between medicines and foods on labeling. Food labels or packaging may not imply that the food has medicinal or therapeutic purposes, or indicate its consumption as a stimulant, to improve health, to prevent diseases, or as having curative action (ANVISA, 2002b). One can conclude, therefore, that a product cannot be classified as food if its label states something like "lowering cholesterol levels", for that is the therapeutic action of hypolipidemic agents. However, one of the functional properties and health claims approved by ANVISA for phytosterols is "*Phytosterols help reduce cholesterol absorption*". Clearly there is a subtle difference between these two phrases, but to the general consumer they may seem the same.

The problem escalates when foreign products are introduced in the country and legal authorities must determine whether they should be classified as food, medicines or neither. To clarify matters, after being officially requested by the DPF, the ANVISA General Office of Medicines issued Technical Note 04/2011 containing guidelines to differentiate medicines from foods. It states that any product, regardless of its nature, that presents therapeutic claims in

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

Table 1
Categories of food similar to dietary supplements in the Brazilian sanitary legislation.

Category	Product legal definition and examples	Legislation
Food for athletes	Specially formulated to achieve specific nutritional needs and improve performance. Examples: whey protein, creatine, Branched-chain amino acids, caffeine.	RDC 18/2010
Vitamin and/or mineral supplement	Foods for supplying the daily intake of vitamins and/or minerals of a healthy person.	Ordinance n° 32/1998
Foods with functional properties or health claims[a]	Functional properties claims: metabolic or physiologic role on growth, development, maintenance and other functions. Health claims: state, suggest or imply a relationship between the food or ingredient with a disease or a health-related condition. Examples: products containing phytosterols, omega-3, lutein and lycopene, inulin, chitosan.	RDC 18/1999
New foods and new ingredients[a]	With no history of consumption in the country, or foods already consumed but containing substances in much higher levels than what is normally present in the diet. Examples: fish oil, soy lecithin, guaraná extract in capsules	RDC 16/1999
Bioactive substances and probiotics with functional properties or health claims[a]	Bioactive substances: nutrients or non-nutrients with specific metabolic or physiologic action. Probiotics: live microorganisms that improve the intestinal microbiologic balance, such as *Bifidobacterium* sp.	RDC 02/2002

[a] Must be registered in the National Health Surveillance Agency prior to marketing (RDC 27/2010). RDC = Resolution of the Executive Board.

its label or package, or that contains substances that are recognizably used for medicinal purposes due to their pharmacological properties, shall be considered as medicines. For example, products containing *Tribulus terrestris* extract "are classified as herbal medicines, for there are medicines registered at ANVISA with this composition". Melatonin, pro-hormones, ephedrine, synephrine, yohimbine and phenethylamines all have pharmacological activities and therefore, a product containing any of these substances should be classified as a medicine. Vasodilation is a pharmacological action and therefore products that claim to increase nitric oxide levels or, by any other means, declare to have vasodilatory properties should also be classified as medicines (ANVISA, 2011a,b).

Products considered supplements elsewhere, but classified as medicines in Brazil, must comply with medicinal laws and norms. According to Law 6.360/1976, updated by Law 10.742/2003, no medicine, including "medicine-supplements", may be sold in Brazil before being registered at ANVISA (BRAZIL, 1976; BRAZIL, 2003); the illegal trade of unregistered medicines is considered a crime against public health. According to the Penal Code (Art. 273), the counterfeiting, adulteration, corrupting or altering of a product intended for therapeutic or medicinal purposes, the sale or distribution of these products, and the sale or distribution of unregistered products are all considered crimes (BRAZIL, 1998).

It is legal to import unregistered products if they are not intended for sale, in amounts compatible with personal use, and if they do not contain proscribed or controlled substances (ANVISA, 2008; ANVISA, 2011b) listed in Ordinance 344/98 (SVS, 1998b) and its updates. However, most individuals are not fully aware of this legislation and its details. For example, dehydroepiandrosterone (DHEA), which is freely marketed in the US, is a controlled substance in Brazil. Dimethylamylamine (DMAA) was proscribed in Brazil in 2012, but buyers may not be aware that euphemisms, such as "geranamine" or "geranium oil", may be used to declare the substance in labels. Consumers may thus end up buying and bringing into the country a proscribed product which has the same legal status as cocaine (ANVISA, 2012).

The full spectrum of the Brazilian legislation is so large that it is not always fully known or understood by law enforcement professionals at national borders and customs offices throughout the country. This leads to the unnecessary seizure of legal products, such as creatine or whey protein, and of products that fall under the category of "unregistered medicines, which are neither controlled nor proscribed, and intended for personal use". To further complicate things, there is no norm stating what amount is considered "compatible with personal use". On the other hand, a single unit of an unregistered medicine may not be brought into the country if it is intended for sale. It is usually not possible for the immigration officer to evaluate on site what the intended use of the product is, especially if small amounts are involved. Consequently, the products may end up being seized, and the involved individual submitted to legal/sanitary sanctions.

3. Adulteration of dietary supplements

The adulteration of dietary supplements with undeclared classic drugs was first mentioned in a FDA's "Safety Alerts for Human Medical Products" in 2002 (USFDA, 2014). Since then, the health authorities of several countries, such as the National Institute for Public Health and the Environment of the Netherlands, Health Canada, and Swiss Medic have reported an increasing number of adulterations (USFDA, 2014; Geyer et al., 2011; Rebiere et al., 2012). The main targets include products indicated for weight loss, body building, and sexual performance enhancement (USFDA, 2011; USFDA, 2011b). These adulterated products may contain approved drugs, analogs or other compounds (such as novel synthetic steroids), and can be found on the internet, and in retail and dietary supplement stores (USFDA, 2011; USFDA, 2011b; Rebiere et al., 2012; Tang et al., 2011; Vaysse et al., 2010).

The presence of an undeclared substance in a supplement may be due to cross-contamination related to poor manufacturing practices and to the use of the same production line for several products. This is usually characterized by the presence of substances that are not necessarily related to the supplement claim (such as traces of steroids in vitamins and minerals), and are present at levels that might not be sufficient for pharmacological action, but may nevertheless lead to a positive result in anti-doping exams (Baume et al., 2006; Geyer et al., 2008, 2011).

The majority of adulteration cases, however, are intentional and aimed at increasing the efficacy of the supplement (Tang et al., 2011; Rebiere et al., 2012). These undeclared drugs may be present at levels that are much higher than those found in approved medicines, representing a health hazard for all consumers (USFDA, 2011; Geyer et al., 2008, 2011). Furthermore, it is not unusual for combinations of up to four or five active substances to be detected in adulterated supplements, which is of particular concern since interaction effects between these substances are not always known (Li et al., 2012; Rebiere et al., 2012).

Fraudulent supplements can cause serious adverse effects in humans, including strokes, acute liver injury, kidney failure, pulmonary embolisms, heart palpitations and death (USFDA, 2011; Vaysse et al., 2010; USFDA, 2013; USFDA, 2013b; Tang et al., 2011; Rebiere et al., 2012). Consumers may not be aware of the presence of drugs and the risk they are taking when consuming these products (USFDA, 2011b).

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

Banned or controlled anorectics such as sibutramine, fenfluramine and diethylpropione can be found in slimming products (Geyer et al., 2011; Tang et al., 2011), and phosphodiesterase-5 inhibitors have been detected in supplements that claim to enhance sexual performance (Gratz et al., 2004). Designer steroids, which are not listed as ingredients in any currently available medication, are now produced exclusively for the nutritional supplement market, even though there is limited or no data regarding their effects and adverse reactions in humans (Geyer et al., 2011).

On its website, the FDA summarizes data on undeclared drug detection in dietary supplements in the US (USFDA, 2014b). The list (first entry in March, 2007) comprised 572 cases up to December 30, 2014, the main product categories being sexual enhancement (238 entries), weight loss (228) and muscle building (90). Sexual enhancement products contained sildenafil, tadalafil, vardenafil and their analogs, alone or in combination. Weight loss products contained mainly sibutramine, associated or not with its analogs or with phenolphthalein, which was also detected alone. Other weight loss drugs included DMAA, fenproporex, furosemide, rimonabant, fenfluramine, cetilistat and phenytoin, among others. Muscle building products contained either an anabolic steroid (not specified) or an aromatase inhibitor (not specified) (USFDA, 2014b).

Another view of the supplement adulteration situation in the US is given by the analysis of data produced by the FDA's MedWatch system, which is responsible for issuing safety alerts on human drugs, medical devices, vaccines and other biologics, dietary supplements and cosmetics. Regarding dietary supplements, these alerts may refer to the risk of adverse effects or drug interactions, bacterial contamination, excessive amounts of toxic substances (such as lead), and undeclared drugs. Data are available on the FDA website from the year 2000 and a summary of alerts issued since 2007 is shown in Table 2. It should be noted that one alert may refer to several different products, and that in nearly all cases the undeclared drug matched the supplement claim (e.g., weight loss products containing anorectic drugs). Until 2009, all supplement alerts were issued in the "Special nutritional and cosmetic products" section. In 2010, the FDA created the specific category of "Products with undeclared drug ingredients: products marketed as dietary supplements, but containing one or more unlisted drug ingredients" (USFDA, 2014).

In the European Union, notifications regarding dietary supplements are made through the Rapid Alert System for Food and Feed (RASFF), in operation since 1979, and available on the RASFF website (European Commission, 2014). From January 1st, 2007 to December 30th, 2014, a total of 929 notification records were found in the system for "dietetic foods, food supplements and fortified foods" (excluding baby and infant food products and notifications related to an industry, but not specifically to a product) (European Commission, 2014). These records are summarized in Table 3.

Over 60% of the RASFF notifications regarded the presence of an unauthorized ingredient, undeclared medicinal drug, and an unauthorized new ingredient (Table 3). The most frequent unauthorized ingredient was DMAA, followed by a variety of herbal extracts, yohimbine, and synephrine. The most frequent medicinal drugs were those related to erectile dysfunction (83 cases; mainly sildenafil, tadalafil and their analogs), and weight management (78 cases; mainly sibutramine). There were also 16 cases of products containing anabolic steroids, such as dehydroepiandrosterone, progesterone and androstenedione. Most of the novel ingredients were herbal extracts, such as *Hoodia gordonii*, *Eurycoma longifolia* (tongkat ali), *Stevia rebaudiana* and noni (European Commission, 2014).

Information regarding the adulteration of foods with drugs in Brazil is limited. Of the 63 Technical Reports issued by ANVISA from 2002 to October, 2014 regarding foodstuffs (ANVISA, 2014b), only two concerned the adulteration of food products with drugs, both cases being sibutramine present in products classified as "new foods and new ingredients" and in "foods for athletes". Searches on the internet found just one other case of adulteration reported by ANVISA, another sibutramine detection in a "new food and/or new ingredient" product. Adverse reactions to medicines, cosmetics and other products, technical complaints and intoxications may be reported by citizens, hospitals, universities, companies and others on the ANVISA Health Surveillance Notification System website (NOTIVISA), (ANVISA, 2014c). However, foodstuffs are not included in the system, hampering the communication between the general public and ANVISA regarding food product adulteration.

Several studies have been published worldwide investigating the presence of synthetic adulterants in dietary supplements, although most were conducted with a limited number of samples. Three studies of "natural slimming products" from Brazil tested 12 to 20 samples and found 30–90% were adulterated with prescription drugs, such as fenproporex, amfepramone, benzodiazepines or furosemide (Almeida et al., 2000; Carvalho et al., 2010; Doménech-Carbó et al., 2013). Studies conducted with samples originating from Japan, China, Syria, USA,UK, Hong Kong, France or "the internet" also found several cases of so-called natural slimming products or dietary supplements adulterated with sibutramine, phenolphthalein, fenfluramine, and other drugs (Vaysse et al., 2010; Tang et al., 2011; Li et al., 2012; Rebiere et al., 2012; Song

Table 2
Summary of United States Food and Drug Administration (FDA) MedWatch Safety Alerts regarding dietary supplements from 2007 to September 2014 (USFDA, 2014).

Year (total)	Alerts
2007 (12)	Possible contamination with *Salmonella*, undeclared sildenafil, tadalafil or their analogs, lovastatine, sibutramine
2008 (9)	Excessive chromium and selenium, presence of ephedra alkaloids, aristolochic acid (carcinogenic and nephrotoxic) or human placenta (cannot be sold as a supplement), undeclared sildenafil analogs, fenproporex, fluoxetine, furosemide, cetilistat.
2009 (4)	Possible contamination with *Salmonella*, risk of side effects, undeclared sildenafil analogs
2010 (24)	Excessive lead, undeclared sildenafil, tadalafil and their analogs, sibutramine and its analogs, steroids, fenfluramine, propranolol and ephedrine
2011 (19)	Possible contamination with *Salmonella*, package identical to a known antibiotic package, undeclared sildenafil, tadalafil and their analogs, sibutramine, superdrol (designer steroid), terazosin (used to treat benign prostatic hyperplasia, in a supplement to "support prostate health")
2012 (16)	Possible contamination with *Salmonella*, undeclared sildenafil, tadalafil and sildenafil analogs, sibutramine, ephedra alkaloids, dexamethasone, diclofenac and methocarbamol (the last three associated in a supplement for arthritis, muscle pain, osteoporosis or bone cancer)
2013 (45)	Undeclared allergens (soy or milk), risk of side effects, presence of DMAA (already forbidden at the time), traces of cloranfenicol (not related to the supplement's alleged purpose), undeclared sibutramine, fluoxetine, sildenafil, tadalafil, vardenafil, dapoxetine, phenolphthalein, methasterone, dimethazine, dimethyltestosterone, non-specified steroids and diuretics, methocarbamol, diclofenac, chlorpromazine, doxepin.
2014 (45)	Possible contamination with *Salmonella* and other microorganisms, undeclared allergen (milk), presence of DMAA, undeclared sildenafil, tadalafil and sildenafil analogs, sibutramine, desmethyl sibrutamine, phenolphthalein, chlorzoxazone, dexamethasone, nefopam, cyproheptadine, diclofenac, ibuprofen, lorcaserin, naproxen, indomethacin, lovastatin, fluoxetine

DMAA: dimethylamylamine.

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

Table 3
Summary of Rapid Alert System for Food and Feed (RASFF) notifications regarding dietary supplements from 2007 to October 2014 (European Commission, 2014).

Year (total)	UNA ingredient	UND drug	UNA new ingredient	UNA irradiation	High levels of metals	Irregular product	Others
2007 (100)	21	11	24	13	7	5	19
2008 (56)	6	9	4	16	4	1	16
2009 (91)	9	19	21	7	8	1	26
2010 (114)	14	35	18	12	8	2	25
2011 (116)	27	39	13	5	5	10	17
2012 (143)	40	42	20	15	9	3	14
2013 (126)	36	28	9	7	18	16	12
2014 (161)	65	33	32	5	10	17	21
TOTAL	218	216	141	80	69	55	150

UNA = unauthorized; UND = undeclared.

et al., 2014). Gratz et al. (2004) found that 19 out of 40 samples of supplements for sexual performance originating from different sources in the USA contained a synthetic phosphodiesterase inhibitor at therapeutic levels.

Geyer et al. (2004) published one of the most comprehensive studies investigating the presence of undeclared substances in dietary supplements. They analyzed 634 non-hormonal supplements originating from 215 companies in 13 different countries, and found that 94 samples (covering nearly all kinds of supplements) contained low levels of prohormones. The authors assumed that, since levels were low, they might have been due to cross-contamination. Other studies detected the presence of anabolic steroids as adulterants in supplements from Switzerland (Baume et al., 2006) and Belgium (Van Poucke et al., 2007), sometimes at levels high enough to be detected in anti-doping exams.

4. The clandestine market in Brazil – products seized by the Brazilian Federal Police Department (DPF)

Information on supplements seized by the DPF was obtained from the DPF Criminalistics System (SisCrim), which was implemented in 2007. The main objectives of the system are the registering of documents, materials related to forensic exams, and to archive forensic reports issued by the criminalistics units. Access to the SisCrim system is restricted to the DPF forensic experts and it allows word searches of its contents. In the present study, a search was conducted to retrieve information on supplements sent for forensic analysis by the DPF between January 1, 2007 and December 31, 2013. The search was first conducted using the keywords *suplemento*, *suplementos*, as well as dietary and supplement. In addition, based on a preliminary search, the keywords *lipo*, *creatina*, creatine, jack3d, pak, nutrition, dymatize, nutrex, dyma, naNO, whey, tribulus, fat and drol were included. All 18 keywords were searched simultaneously using the logical operator "or".

Data obtained from the reports included the year and state where they were issued, name and brand of the products, country of declared origin, and conclusions. More than one product may be included in a given report, and one product may be comprised of several identical units. When available, results of chemical analyses were also obtained from the reports. All analyses were qualitative, performed by forensic experts using screening methods by Gas Chromatography–Mass Spectrometry (Agilent Technologies, GC 6890N coupled with MS 5973 Inert or GC 7890A coupled with MS 5975C) and/or Infrared Spectrometry with Fourier Transform (Thermo Scientific, FT-IR Spectrometer Nicolet iS10, Nicolet 380 or Nicolet Nexus 470). In certain cases, it was also necessary to perform a specific DMAA-confirmation analysis by Liquid Chromatography–Time-of-Flight Mass Spectrometry (LC-MSD TOF, Agilent Technologies 1100 Series). These methods are routinely used by the DPF laboratories in forensic analyses.

The SisCrim search produced 1222 forensic reports, which included the results of 5470 products classified as supplements. There was an upward trend in the number of reports that included supplements and of products over the years, increasing from 13 reports (118 products) in 2007 to 402 reports (1590 products) in 2013. Considering the total number of forensic reports issued by the DPF (including other forensic fields), reports containing supplement data ranged from 0.35‰ of all reports in 2007 to 9.02‰ in 2013.

The reports were issued by the criminalistics units of 20 of the 26 Brazilian states and of the Federal District. The majority of products was seized in the states of *Paraná* and *São Paulo* (34.6 and 22.4%, respectively), followed by *Mato Grosso do Sul* (10.9%) and *Ceará* (9.6%). These results were expected given that 94.8% of products were of declared foreign origin (92.5% declared to be manufactured in/by the US): *Paraná* and *Mato Grosso do Sul* are states bordering Paraguay, from which most illegal products enter the country, and *São Paulo* is where the main Brazilian international airport is located.

4.1. Supplement categories and products

Once individualized by name and brand, the search revealed 1535 different supplement products, which were classified into categories according to their declared composition and information on the packaging. Some of these products were further divided into subcategories. The categories, their characteristics, and the number of products seized are shown in Table 4. In cases where the claims of the product did not reflect the composition shown on the label, the classification was made based on the declared composition. For example, a product containing only amino acids, but that claimed to "increase the amount of circulating testosterone", was classified as an amino acid.

The most frequent products found in the reports were slimming/energy (SLIM) items, also known as fat burners, accounting for 23.5% of the products (Table 4). These were followed by hormone modulators (MOD; 17.1%), and by those in the vasodilator/volumizer category (VASO; 16.1%), also known as pre-workout products. Among the products classified as having a defined therapeutic action (N = 297, Table 4), the most frequent were those recommended to promote better sleep (N = 105) and joint rebuilders (N = 78), followed by those claiming to "improve the circulatory system" and diuretics (N = 19 and 18, respectively). Among products classified as herbal (N = 125), most claimed to have a positive effect on concentration and mental focus (N = 26), followed by those recommended for prostatic hyperplasia (N = 15), immune system adjuvants (N = 14), and antioxidants (N = 12).

Fig. 1 shows the percentages of the main supplement categories seized over the period of the study. SLIM accounted for 19–34% of all products over the entire period. MOD and VASO supplements have "gained importance" over the years (from 7.6% of all products in 2007 to 43% in 2013), while amino acids and vitamins/minerals

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

Table 4
Dietary supplement products seized by the Brazilian Federal Police Department (DPF) from 2007 to 2013, classified by category.

Category (example)	Characteristics of the products	N (% of total)
SLIM (Lipo 6 Black®)	Indicated for weight loss (*fat burners*), usually containing central nervous system stimulants	1285 (23.5%)
MOD (DHEA®, M-Drol®)	Anabolic-androgenic steroid precursors (pro-hormones), claiming to increase endogenous steroids	938 (17.1%)
VASO (Jack3d®)	"Pre-workout", claim to provide energy and promote vasodilation and/or increase muscle cell volume	880 (16.1%)
Amino acid (BCAA, creatine)	One or few amino acids, or amino acid products	665 (12.2%)
Vitamin/mineral (Centrum®)	Containing vitamins and/or minerals	460 (8.4%)
Protein (*Whey protein*)	Containing only or mainly proteins	366 (6.7%)
Therapeutic Action (Osteo Bi-Flex®, Melatonin®)	Claiming specific therapeutic action, excluding weight loss or anabolism, such as joint repair, diuretic or sleep improvement.	297 (5.4%)
Multifunctional (Animal Pak®)	Small plastic bag with several pills/capsules, a complex formulation and several claims	202 (3.7%)
Herbal (Ginkgo Plus®, Green Tea®)	Plant extracts (with exception of *Tribulus terrestris*); usually with well defined therapeutic claims.	125 (2.3%)
Oil (Omega 3-6-9®)	Containing only fatty acids	41 (0.7%)
Meal replacements (Lean Mass®)	Containing carbohydrates, proteins and sometimes fat; controlled calories	38 (0.7%)
Hypercaloric (Mega Gainer®)	Containing carbohydrates, proteins and fat; high calories	37 (0.7%)
Carbohydrate (Carb Up®)	Containing simple carbohydrates, such as maltodextrin	33 (0.6%)
(Natural Gelatin®)	Indicated to nourish the hair, skin or nails	20 (0.4%)
Antioxidant (Cell Guard®)	Non-herbal products with purported anti-oxidant activity	19 (0.3%)
Probiotic (AcidoPhilus®)	Containing microorganisms that are believed to improve health	10 (0.2%)
Recovery (After FX®)	Supposedly improve recovery after exercising	10 (0.2%)
Others	None of the previous categories, include soy lecithin and chitosan	44 (0.8%)

SLIM: slimming/energy; MOD: hormone modulators; VASO: vasodilator/volumizer.

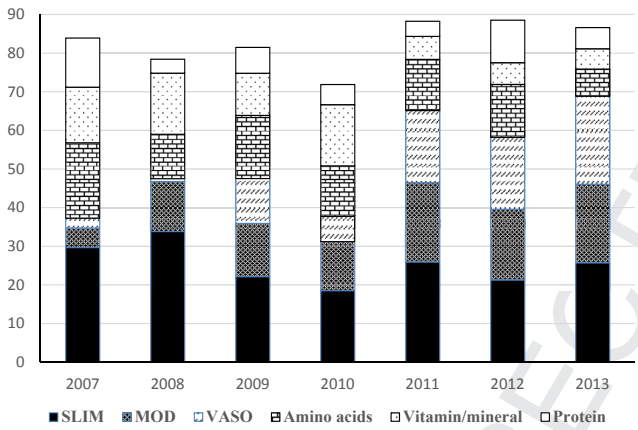

Fig. 1. Percentages of the main supplement categories seized by the Brazilian Federal Police Department from 2007 to 2013 (SLIM = slimming/energy; VASO = vasodilator/volumizer; MOD = hormone modulator).

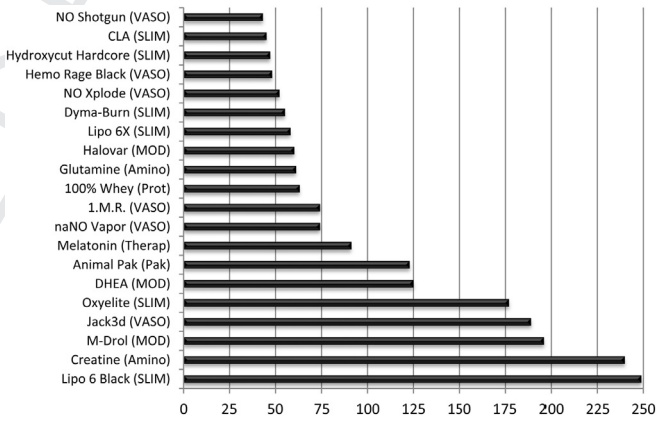

Fig. 2. Most frequent products seized by the Brazilian Federal Police Department from 2007 to 2013 individualized by name, independent of the brand. SLIM = slimming/energy; VASO = vasodilator/volumizer; MOD = hormone modulator; Amino = amino acid; Pak = multifunctional pak; Therap = therapeutic action; Prot = protein.

proteins showed a tendency of "losing importance" with time.

The 5470 products analyzed were individualized by name, regardless of the brand. Of the twenty most frequent products, seven were VASO, six SLIM, and three MOD (Fig. 2). The most frequent products were Lipo 6 Black (SLIM, N = 249), and Creatine (Amino acid, N = 240).

4.2. Chemical analyses and adulterations

The DPF has no standard procedure for the forensic evaluation of dietary supplements. When deemed necessary by the forensic expert, chemical analyses were performed of the seized products. Between 2007 and 2011, most products (N = 2898, 53%) were chemically analyzed, a percentage that has increased over the years (from 17.8% in 2007 to 58.7% in 2013), reaching a maximum in 2011 (75.3%). All analyses were qualitative, and most were non-specific screenings (except DMAA-confirming analysis) aimed mainly at the detection of undeclared synthetic drugs. Hence, products could only be considered adulterated when an undeclared substance was detected or when the product did not contain a declared substance and such substance was known to be detectable by the techniques used. In total, 180 adulteration cases were detected (6.2% of analyzed products), with a steady increase in the number of adulterations detected over the years, reaching almost 10% of all products chemically analyzed in 2013. The origin of adulterated products was related to the origin of all products (92.2% of adulterated products with declared north-American origin; 5% of adulterated products were of declared Brazilian origin).

The types of adulteration, their definitions, and the number of products are listed in Table 5. In 41.1% of the cases, the product contained an undeclared drug related to what was claimed on the labeling, mainly anabolic steroids, anorectics or phosphodiesterase inhibitors. Undeclared drugs from other therapeutic classes (mainly caffeine and anti-inflammatory drugs in MOD products) accounted for 21.7% of the cases. Since all analyses were qualitative, it was not possible to determine the concentration of the substances detected. In most cases, the detected substance was shown as a significant peak in the GC–MS analysis, and no forensic report mentioned needing to concentrate the sample in order to detect undeclared drugs.

About 60% of the MOD and SLIM products were chemically analyzed, accounting for 95.6% of the adulterated products (132 and 40 products, respectively). Among the MOD, 39.4% had an undeclared related drug (such as turinabol, oxymetholone and

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

Table 5
Types of adulterations found in the supplements chemically analyzed by the Brazilian Federal Police Department (DPF) from 2007 to 2013 (total of 180 adulterated products).

Type	Examples	N (%)
Undeclared pharmacologically related drugs	Presence of anabolic steroids in MOD (oxymetholone, metandienone or oral turinabol), presence of anorectics in SLIM (sibutramine, fenproporex), presence of phosphodiesterase inhibitors in herbal products indicated to enhance masculine sexual performance (tadalafil)	74 (41.1)
Undeclared drug of another therapeutic class	MOD or anti-aging product that only contained caffeine	39 (21.7)
Incomplete formulation	Suppression of listed ingredient, such as Oxyelite Pro containing only yohimbine, but not the declared caffeine and DMAA.	29 (16.1)
Absence of active ingredients	Amino acid product containing only starch	24 (13.3)
Replacement by structurally similar substances	Replacement of pro-hormones such as halodrol, methasterone and dienedione by dehydroepiandrosterone, 16,17-epoxyprogesterone or 16-dehydroprogesterone	14 (7.8)

SLIM: slimming/energy; MOD: Hormone modulators; DMAA: dimethylamylamine; BCAA: branched-chain amino acid.

metandienone), 28.0% contained undeclared substances of another therapeutic class (mainly caffeine, with five dipyrone and two aminopyrine detections), and 16.7% had no active substance whatsoever. Of the 40 SLIM adulterated products, 55.0% did not contain all the substances declared on the package and 42.5% had an undeclared related medicine (such as sibutramine, fenproporex, phenolphthalein or amfepramone). The other eight adulterated products were: three therapeutic action products (all for sexual enhancement, containing phosphodiesterase inhibitors), two multifunctional paks that claimed to increase muscles and contained undeclared pro-hormones, one protein product containing sibutramine, one amino acid product containing only starch, and one product classified in the "others" category, with purported anti-aging properties, but containing only undeclared caffeine (Table 5).

The adulteration rate for the MOD category was 22.1% (597 products, 132 adulterations), whereas SLIM products had a far lower rate of 5.2% (766 products, 40 adulterations). Out of the six analyzed products with a declared therapeutic action of male sexual enhancement, three were adulterated.

Most of the adulterations (68.9%) concerned only five products: Halovar (MOD; N = 39), M-Drol (MOD; N = 31), Oxyelite Pro (SLIM; N = 26), Reign (MOD; N = 17) and D-Drol (MOD, N = 11). It was not possible to determine if these adulterated products were from the original manufacturer, or whether they were counterfeits made in clandestine facilities as the original packaging was not available at the forensic laboratory.

5. Discussion

In most part of the world medicines tend to be more strictly regulated than food products (McCann, 2005; Brownie, 2005; Eussen et al., 2011; Lachenmeier et al., 2012; Coppens et al., 2006). There is no simple way of regulating dietary supplements, and determining whether dietary supplements are food, medicines, or fall in an "in-between" category is an issue of the utmost importance to decide which legal norms apply to these products.

Brazilian legislation is similar to the EU in several aspects, but both are more restrictive in comparison with US legislation for requiring pre-market registration for some supplements freely marketed in US. In Brazil, "herbal supplements" must be registered as phytotherapic medicines (such as those containing St John's Wort or *T. terrestris* extract) or, in some cases, as "new foods and new ingredients". In both situations, the safety of the product must be attested to by the registration authority. One example of a Brazilian legislation restriction regards green tea extract in capsules, which is not allowed in Brazil, although green tea is freely available as a food. According to ANVISA, "capsule" is a new presentation of green tea, and must be registered as a new food, requiring evidence of its safety (ANVISA, 2010c).

Brazil, United States and the European Union forbid the presence of medical claims (stating that the product can prevent, treat or cure a disease) in food product packaging or labeling, but allow such claims for medical products (EC, 2000; USA, 1994; Eussen et al., 2011). Food products may present nutrition or health claims, such as "Phytosterol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease". It is not allowed, however, to state "phytosterol esters reduce the risk of coronary heart disease", a subtle distinction, even though this conclusion is easily reached by most consumers who read the approved health claim (Eussen et al., 2011).

The vitamins and/or mineral supplements category is apparently well-defined in Brazil and the European Union. While in Brazil these products must contain between 25 and 100% of the Recommended Daily Intake (SVS, 1998), in Europe the maximum amount should take into account the upper safe levels and intakes from other dietary sources. US legislation, on the other hand, does not mention any maximum amount of vitamins and/or minerals in supplements.

In Brazil, certain categories of food, such as those with functional properties or health claims, have positive lists of substances that can be legally present. On the other hand, the permissive nature of the US DSHEA and the non-publication of additional regulation established by EU Directive 2002/46/EC may produce borderline products on their respective markets. Brazil and the EU explicitly forbid the presence of substances with therapeutic action in products sold as food. However, legislation in certain European countries may grant a different status to a given product. Determining whether a product has or does not have therapeutic action may be difficult in some cases, and it is an issue that EU is trying to address by adopting the homeostasis model. The US allows several products with therapeutic action to be marketed as dietary supplements, as long as they have been in use before the enactment of the DSHEA in 1994 and bear a sentence stating that such products are not intended to diagnose, treat, cure or prevent diseases.

Data on supplement products seized by the DPF from 2007 to 2013 showed that most were slimming products (SLIM), hormone modulators (MOD) and vasodilators/volumizers (VASO). Practically no product in these categories may be commercialized in Brazil as a supplement, as they contain substances with therapeutic purposes, stimulants, and/or contain more than 100% of the RDI of a vitamin or mineral. Differences in legislation between countries mean that many of these products are legally available abroad, but because Brazilian legislation is confusing and scattered, Brazilian travelers may not be aware that some products are considered medicines or even proscribed in Brazil.

SLIM and MOD products make similar claims, and sometimes have similar composition as medicines with anabolic and anorectic actions. Both therapeutic classes are subject to control by ANVISA, and cannot be obtained in Brazil without a prescription. The fact that these were the two most frequently seized categories by the

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

DPF suggests that consumers are replacing anabolic steroids and anorectic medicaments with dietary supplements that have allegedly similar functions.

Results from the DPF suggest that the market reacts positively to regulation, when new products are approved. This phenomenon became very evident with products containing only creatine, whose seizures diminished significantly after the approval of creatine as food for athletes by RDC 18/2010 (6% of all products in 2009 and 2.1% in 2013). On the other hand, DMAA was banned in Brazil in 2012 (ANVISA, 2012), but the two most frequently seized products in 2013 were Oxyelite Pro and Lipo 6 Black, both containing DMAA (15% of the total seized that year). While the creatine case illustrates the positive effect of regulation on the clandestine market, the case of DMMA and others indicate that this market is not inhibited by regulation nor even by proscription as long as there is a consumer demand for the product.

The fact that supplements are commercialized as "food" leads consumers to perceive that they are harmless and devoid of adverse effects (McCann, 2005; Vaysse et al., 2010; Tang et al., 2011), and the adverse effects are rarely mentioned on the product label. Even ingredients common in supplements, such as caffeine, creatine or Ginkgo Biloba, can lead to serious adverse effects (Bove, 2002; Eudy et al., 2013; Sepkowitz, 2013). Herbal extracts in supplements have been implicated in cases of liver injury, allergic reactions, toxic reactions and drug interactions, sometimes resulting in death (Ernst, 1998; Navarro and Seeff, 2013; Timcheh-Hariri et al., 2012). MOD products may be associated with all adverse effects related to anabolic steroid consumption, including masculinization in women, hepatotoxicity, and alteration of blood lipid levels and coagulation factors (Shahidi, 2001; Kicman, 2008). DMAA was banned in Brazil and other countries due to, among others, cases of cerebral hemorrhage and deaths associated with its intake (Eliason et al., 2012; Gee et al., 2012; Health Canada, 2011; USFDA, 2013b).

However, due to certain restrictive aspects of Brazilian legislation, products with otherwise "harmless" formulations may be considered irregular or classified as medicines. For example, according to RDC 18/2010, caffeine supplements for athletes must not contain "nutrients or other non-nutrients", and therefore a product containing a mixture of creatine and caffeine is considered an "unauthorized association". Likewise, although protein and branched-chain amino acid (BCAAs) supplements are legal, adding BCAAs to a protein supplement is not allowed. This was the case with Isofast-MHP, whose distribution and sale was forbidden in the country (ANVISA, 2014d).

The adulteration of dietary supplements, mainly by the inclusion of undeclared drugs or other non-approved ingredients, is another point of concern. Its occurrence has been well documented abroad over the past decade, and both the US and EU sanitary authorities have systems informing consumers of the detection of adulterated products (Tables 2 and 3). Brazil does not have a comparable notification system, since the NOTIVISA does not include foodstuffs. Data reported by the FDA and the RASFF indicate that the number of adulterations detected over the past years has remained stable or increased slightly. As the total number of products evaluated was not available, it was not possible to determine if the adulteration rates were actually increasing.

In general, investigations on supplement adulterations published in the literature have focused on target products to detect undeclared drugs, mainly anorectics, anabolic steroids or drugs for erectile dysfunctions. Few studies have been published in Brazil in this area, and they usually refer to the investigation of anorectics in herbal formulations. Considering the nine adulterated products found in this study whose declared origin was Brazil, five were SLIM products containing sibutramine (3 cases), femproporex or an association of chlordiazepam and fluoxetine, one was a protein product also containing sibutramine, and the three others contained caffeine, being two MOD and one in the "others" category.

The overall adulteration rate of the supplement products analyzed by the DPF from 2007 to 2013 was 6.2% (180 cases), with 78 cases of undeclared medicinal drugs, a number much lower than that notified to the FDA (474) and to the RASFF (183) for the same period. It was not possible to ascertain whether these higher numbers are due to a higher adulteration rate, a larger total supplement market or to a more efficient adulteration detection and reporting system. It is possible that the Brazilian figure is underestimated due to the nature of the chemical analyses performed by the DPF (discretionary, qualitative, mainly general-screening). It is reasonable to hypothesize, however, that a less restrictive legal framework could lead to more adulteration cases, since there are fewer control mechanisms, a case in point being the US, where the registry or even the reporting of the intention of placing a product on the market is not required, except for those with a new dietary ingredient.

The major targets for adulteration differ between countries. While in the US and the EU muscle-building products were the least frequent targets for adulteration (9.1 and 4.4% of adulterated products, respectively), in Brazil these products accounted for 73% of all adulterations. The adulteration rate for MOD products found in this study was 22.1%. Products for sexual enhancement accounted for 42.6% of all notifications in the US and 39.3% in the EU, while in Brazil they represented only 4% of adulterated products (only 9 seized products had declared sexual enhancement properties). It is possible that the low incidence of these supplements in Brazil is a consequence of the Brazilian clandestine market of medicines containing substances for erectile dysfunction. These medicines were the most frequently analyzed by DPF forensic experts, and were also the main targets for counterfeiting, representing 46.1% of all counterfeits detected by the DPF from 2006 to 2012 (Marcheti, 2014). Drugs for erectile dysfunction require prescriptions to be purchased in Brazil, the US and the EU. Nevertheless, the product is generally freely sold at Brazilian pharmacies. Therefore, as these products are widely available both on the regular and the clandestine market in Brazil, there is no significant demand for supplements with these characteristics.

The consumption of an adulterated product poses an additional health risk since consumers do not know what substances they are ingesting. The unrecognized use of drugs such as tadalafil (for erectile dysfunction), sibutramine (an anorectic), or oral turinabol (an anabolic steroid), all of which were detected in some of the products analyzed by the DPF, may not only lead to adverse effects inherent to these substances, but also to more unforeseeable effects due to association with other drugs a given individual may be consuming. Unfortunately, a quantitative analysis was not performed by the DPF which would allow a more precise evaluation of the potential adverse effects.

The main limitations of the DPF data investigated in this study were that not all the seized samples were chemically analyzed, that the analyses performed were mostly general-screening, and were all qualitative. Adulterations due to the presence of an active ingredient at a different concentration from what was declared could not be detected, although this information was not always stated in the label. The complexity of some supplements was also a great challenge, since analytical methods that could detect every substance declared were not available at the DPF forensic laboratories, and therefore cases of supplements lacking declared substances could not always be detected. Furthermore, data originating from the DPF refer mainly to products seized at the country's borders or at post offices, and cannot be extrapolated to fully represent the overall Brazilian situation. On the other hand, to the best of our knowledge, the information provided in this study

reflects the largest data available on detection of adulterated supplements in the literature, including products classified as medicines according to current legislation, as most studies were restricted to a much smaller number of samples.

6. Conclusion

Dietary supplements comprise a wide variety of products that fall under different regulatory frameworks worldwide. Although US legislation may be considered more permissive, Brazil's more restrictive, with the EU lying in between, the respective legal frameworks have not proven to be very effective in dealing with all the products available on the market or with preventing the distribution and sale of adulterated or irregular products. The US had the highest number of supplement adulteration notifications during the period from 2007 to 2013, which may be a consequence of a larger market when compared with other countries, an aspect that was not evaluated in this study. Brazil does not have a notification system, so the present study, based on products sent to forensic analysis by the DPF, is the first to estimate the incidence and profiles of adulterated and irregular supplements on the Brazilian market.

In this study, we could not establish the adulteration rates for dietary supplements in Europe (RASFF) and the USA (FDA) due to the lack of information on the total number of samples tested in each dataset. Most likely, because of these limitations, the calculated Brazilian adulteration rate of 6.2% is underestimated. Hence, any quantitative comparison of adulteration rates between Europe, USA and Brazil is not possible with the available data. However, the rising numbers of notifications from the FDA and RASFF, as well as the rising trend observed in data coming from the DPF, suggest that either the adulteration problem is increasing or that detection mechanisms are improving. Educating the public regarding the potential risks they are taking when consuming adulterated or irregular products is essential to protect human health. Public education could also decrease the demand for adulterated and irregular products with a significant impact on the illegal market.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2015.06.013.

Uncited reference

Q3

ANVISA, 2002a.

References

Almeida, A.E., Ribeiro, M.L., Polese, L., 2000. Determination of Amfepramone Hydrochloride, Fenproporex, and Diazepam in so-called “Natural” Capsules used in the Treatment of Obesity, vol. 23. Rel. Tech, pp. 1109–1118 (Accessed 29.09.14.).

ANVISA (Brazilian Sanitary Surveillance Agency), 1999a. Resolução – RDC n° 16, de 30 de abril de 1999 – Aprova o Regulamento Técnico de procedimentos para registro de alimentos e ou novos ingredientes, constante do anexo desta Portaria.

ANVISA (Brazilian Sanitary Surveillance Agency), 1999b. Resolução – RDC n° 18, de 30 de abril de 1999 – Aprova o Regulamento Técnico que estabelece as diretrizes básicas para análise e comprovação de propriedades funcionais e ou de saúde alegadas em rotulagem de alimentos.

ANVISA (Brazilian Sanitary Surveillance Agency), 2002a. Resolução – RDC n° 02, de 07 de janeiro de 2002 – Aprova o Regulamento Técnico de substâncias bioativas e probióticos isolados com alegação de propriedades funcional e ou de saúde.

ANVISA (Brazilian Sanitary Surveillance Agency), 2002b. Resolução – RDC n° 259, de 20 de setembro de 2002 – Aprova o Regulamento sobre rotulagem de alimentos embalados.

ANVISA (Brazilian Sanitary Surveillance Agency), 2008. Resolução – RDC n° 81, de 05 de novembro de 2008 – Dispõe sobre o Regulamento Técnico de Bens e Produtos Importados para fins de Vigilância Sanitária.

ANVISA (Brazilian Sanitary Surveillance Agency), 2010a. Resolução – RDC n° 18, de 27 de abril de 2010 – Dispõe sobre alimentos para atletas.

ANVISA (Brazilian Sanitary Surveillance Agency), 2010b. Resolução – RDC n° 27, de 06 de agosto de 2010 – Dispõe sobre as categorias de alimentos e embalagens isentos e com obrigatoriedade de registro sanitário.

ANVISA (Brazilian Sanitary Surveillance Agency), 2010c. Informe Técnico n° 45, de 28 de dezembro de 2010 – Esclarecimentos sobre a regulamentação de chás.

ANVISA (Brazilian Sanitary Surveillance Agency), 2011a. Gerência Geral de Medicamentos. Nota Técnica n° 4, de 07 de janeiro de 2011.

ANVISA (Brazilian Sanitary Surveillance Agency), 2011b. Resolução – RDC n° 28, de 28 de junho de 2011 – Altera dispositivos da Resolução de Diretoria Colegiada – RDC n° 81, de 5 de novembro de 2008, que aprovou o Regulamento Técnico de Bens e Produtos Importados para fins de Vigilância Sanitária.

ANVISA (Brazilian Sanitary Surveillance Agency), 2012. Resolução – RDC n° 37, de 02 de julho de 2012-Dispõe sobre a atualização do Anexo I, Listas de Substâncias Entorpecentes, Psicotrópicas, Precursoras e Outras sob Controle Especial, da Portaria SVS/MS n° 344, de 12 de maio de 1998 e dá outras providências.

ANVISA (Brazilian Sanitary Surveillance Agency), 2014a. Resolução – RDC n° 26, de 13 de maio de 2014 – Dispõe sobre o registro de medicamentos fitoterápicos e o registro e a notificação de produtos tradicionais fitoterápicos.

ANVISA (Brazilian Sanitary Surveillance Agency), 2014b. Alimentos/Assuntos de Interesse/Informes Técnicos. Updated on October 2, 2014. http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Alimentos/Assuntos+de+Interesse/Informes+Tecnicos (Accessed 06.10.14.).

ANVISA (Brazilian Sanitary Surveillance Agency), 2014c. NOTIVISA – Sistema de Notificações em Vigilância Sanitária. Updated on May 26, 2014. http://www.anvisa.gov.br/hotsite/notivisa/relatorios/index.htm (Accessed 24.11.14).

ANVISA (Brazilian Sanitary Surveillance Agency), 2014d. Resolução – RE n° 572, de 14 de fevereiro de 2014.

Baume, N., Mahler, N., Kamber, M., Mangin, P., Saugy, M., 2006. Research of stimulants and anabolic steroids in dietary supplements. Scand. J. Med. Sci. Sports 16, 41–48.

Bove, A.A., 2002. Dietary supplements in athletes. Am. Coll. Card. Cur. J. Rev. Jan/Feb, 18–20. Q2

BRAZIL, 1969. Decreto-Lei n. 986, de 21 de outubro de 1969. Institui normas básicas sobre alimentos. Diário Oficial da União, p. 8935 retificação em 11 de novembro de 1969, p. 9737.

BRAZIL, 1973. Lei n. 5.991, de 17 de dezembro de 1973. Dispõe sobre o controle sanitário do comércio de drogas, medicamentos, insumos farmacêuticos e correlatos, e dá outras providências. Diário Oficial da União, p. 13049 retificação em 21 de dezembro de 1973, p. 13182.

BRAZIL, 1976. Lei n. 6.360, de 23 de setembro de 1976. Dispõe sobre a Vigilância Sanitária a que ficam sujeitos os medicamentos, as drogas, os insumos farmacêuticos e correlatos, cosméticos, saneantes e outros produtos, e dá outras providências. Diário Oficial da União, p. 12647.

BRAZIL, 1998. Lei n. 9.677, de 02 de julho de 1998. Altera dispositivos do Capítulo III do Título VIII do Código Penal, incluindo na classificação dos delitos considerados hediondos crimes contra a saúde pública, e dá outras providências, vol. 1. Diário Oficial da União, Seção, p. 1 (03/07/1998).

BRAZIL, 2003. Lei n. 10.742, de 06 de outubro de 2003. Define normas de regulação para o setor farmacêutico, cria a Câmara de Regulação do Mercado de Medicamentos – CMED e altera a Lei n° 6.360, de 23 de setembro de 1976, e dá outras providências, vol. 1. Diário Oficial da União, Seção, p. 1 (07/10/2003).

Brownie, S., 2005. The development of the US and Australian dietary supplement regulations – what are the implications for product quality? Comp. Ther. Med. 13, 191–198.

Carvalho, L.M., Correia, D., Garcia, S.C., Bairros, A.V., Nascimento, P.C., Bohrer, D., 2010. A new method for the simultaneous determination of 1,4-benzodiazepines and amfepramone as adulterants in phytotherapeutic formulations by voltammetry. For. Sci. Int. 202, 75–81.

Carvalho-Silva, L.B., Braga, G.G., Lollo, P.C.B., 2012. Utilização de suplemento alimentar e anabolizante por praticantes de musculação nas academias de Goiânia-GO. Rev. Bras. Nutr. Clin. 27, 158–163.

Cohen, P.A., 2012. DMAA as a dietary supplement ingredient. Arch. Int. Med. 9 (172), 1038–1039.

Coppens, P., Delmulle, L., Gulati, O., Richardson, D., Ruthsatz, M., Sievers, H., Sidani, S., 2006. Use of botanicals in food supplements. Ann. Nutr. Met. 50, 538–554.

Coppens, P., Silva, M.F., Pettman, S., 2006b. European regulations on nutraceuticals, dietary supplements and functional foods: a framework based on safety. Toxicology 221, 59–74.

Corby-Edwards, A.K., 2013. Regulation of Dietary Supplements. Congressional Research Service, p. R43062. www.ces.gov.

CE (Council of Europe), 2008. Homeostasis, a Model to Distinguish between Foods (Including Food Supplements) and Medicinal Products. Partial Agreement in the Social and Public Health Field. Council of Europe, Strasbourg, France.

Damiano, F., Silva, C., Gregori, A., Vacondio, F., Mor, M., Menozzi, M., Di Giorgio, D., 2014. Analysis of illicit dietary supplements sold in the Italian market: identification of a sildenafil thioderivative as adulterant using UPLC-TOF/MS and GC/MS. Sci. Justice 54, 228–237.

De Rose, E.H., Feder, M.G., Pedroso, P.R., Guimarães, A.Z., 2006. Referred use of medication and dietary supplements in athletes selected for doping control in the South-American games. Rev. Bras. Med. Esporte 12, 239–242.

Diehl, K., Thiel, A., Zipfel, S., Mayer, J., Schnell, A., Schneider, S., 2012. Elite adolescent athletes' use of dietary supplements: characteristics, opinions, and sources

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

of supply and information. Int. J. Sport Nutr. Exerc. Met. 22, 165–174.
Doménech-Carbó, A., Martini, M., Carvalho, L.M., Viana, C., Doménech-Carbó, M.T., Silva, M., 2013. Screening of pharmacologic adulterant classes in herbal formulations using voltammetry of microparticles. J. Pharm. Biomed. Anal. 74, 194–204.
Eliason, M.J., Eichner, A., Cancio, A., Bestervelt, L., Adams, B.D., Deuster, P.A., 2012. Case reports: death of active duty soldiers following ingestion of dietary supplements containing 1,3-dimethylamylamine (DMAA). Mil. Med. 177, 1455–1459.
Ernst, E., 1998. Harmless herbs? A review of the recent literature. Am. J. Med. 104, 170–178.
Eudy, A.E., Gordon, L.L., Hockaday, B.C., Lee, D.A., Lee, V., Luu, D., Martinez, C.A., Ambrose, P.J., 2013. Efficacy and safety of ingredients found in preworkout supplements. Am. J. Health Sys. Pharm. 70, 577–588.
European Commission, 2014. Rapid Alert System for Food and Feed (RASFF) Portal. https://webgate.ec.europa.eu/rasffwindow/portal/?event=SearchForm&cleanSearch=1 (Access on December 30, 2014).
EEC (European Economic Community), 1965. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products. Off. J. 022, 0369–0373.
EC (European Parliament and European Council), 2000. Directive 2000/13/EC of the European Parliament and of the Council of 20 March 2000 on the approximation of the laws of the member states relating to the labelling, presentation and advertising of foodstuffs. Off. J. Eur. Comm. L109, 29–42.
EC (European Parliament and European Council), 2001. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Off. J. Eur. Comm. L311, 67–128.
EC (European Parliament and European Council), 2002. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the member states relating to food supplements. Off. J. Eur. Comm. L183, 51–57.
EC (European Parliament and European Council), 2002b. Regulation 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European food safety authority and laying down procedures in matters of food safety. Off. J. Eur. Comm. L31, 1–24.
EC (European Parliament and European Council), 2004. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the community code relating to medicinal products for human use. Off. J. Eur. Comm. L136, 34–57.
EC (European Parliament and European Council), 2006. Regulation 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off. J. Eur. Comm. L404, 9–25.
EC (European Parliament and European Council), 2006b. Regulation 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. Off. J. Eur. Comm. L404, 26–38.
Eussen, S.R.B.M., Verhagen, H., Klungel, O.H., Garssen, J., van Loveren, H., van Kranen, H.J., Rompelberg, C.J.M., 2011. Functional foods and dietary supplements: products at the interface between pharma and nutrition. Eur. J. Pharm. 668, S2–S9.
Fayh, A.P.T., Silva, C.V., Jesus, F.R.D., Costa, G.K., 2013. Consumption of nutritional supplements among individuals in Porto Alegre's fitness centers. Rev. Bras. Cien. Esporte 35, 27–37.
Finley, J.W., Finley, J.W., Ellwood, K., Hoadley, J., 2014. Launching a new food product or dietary supplement in the United States: industrial, regulatory, and nutritional considerations. Ann. Rev. Nutr. 34, 421–447.
Gee, P., Tallon, C., Long, N., Moore, G., Boet, R., Jackson, S., 2012. Use of recreational drug 1,3-dimethylethylamine (DMAA) associated with cerebreal hemorrhage. Ann. Emerg. Med. 60, 431–444.
Geyer, H., Braun, H., Burke, L.M., Stear, S.J., Castell, L.M., 2011. A–Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance—part 22. Br. J. Sports Med. 45, 752–754.
Geyer, H., Parr, M.K., Mareck, U., Reinhart, U., Schrader, Y., Schänzer, W., 2004. Analysis of non-hormonal nutritional supplements for anabolic-androgenic steroids - results of an international study. Int. J. Sports Med. 25, 124–129.
Geyer, H., Parr, M.K., Koehler, K., Mareck, U., Schänzer, W., Thevis, M., 2008. Nutritional supplements cross-contaminated and faked with doping substances. J. Mass Spectr. 43, 892–902.
Goston, J.L., Correia, M.I.T.D., 2010. Intake of nutritional supplements among people exercising in gyms and influencing factors. Nutrition 26, 604–611.
Gratz, S.R., Flurer, C.L., Wolnik, K.A., 2004. Analysis of undeclared synthetic phosphodiesterase-5 inhibitors in dietary supplements and herbal matrices by LC–ESI–MS and LC–UV. J. Pharm. Biomed. Anal. 36, 525–533.
Health Canada, Health Products and Food Branch, 2011. Classification of 1,3 Dimethylamylamine (DMAA). http://pt.scribd.com/doc/82744576/DMAA-Health-Canada-2011.
Jacobson, I.G., Horton, J.L., Smith, B., Wells, T.S., Bouko, E.J., Lieberman, H.R., Ryan, M.A.K., Smith, T.C., 2012. Bodybuilding, energy, and weight-loss supplements are associated with deployment and physical activity in U.S. military personnel. Ann. Epidem. 22 (5), 318–330.
Kicman, A.T., 2008. Pharmacology of anabolic steroids. Br. J. Pharmacol. 154, 502–521.
Kristiansen, M., Levy-Milne, R., Barr, S., Flint, A., 2005. Dietary supplement use by varsity athletes at a Canadian university. Int. J. Sport Nutr. Exerc. Met. 15, 195–210.
Lachenmeier, D.W., Steffen, C., El-Atma, O., Maixner, S., Löbell-Behrends, S., Kohl-Himmelseher, M., 2012. What is a food and what is a medicinal product in the European Union? Use of the benchmark dose (BMD) methodology to define a threshold for "pharmacological action". Regul. Toxicol. Pharmacol. 64, 286–295.
Lachenmeier, D.W., Löbell-Behrends, S., Böse, W., Marx, G., 2013. Does European Union food policy privilege the internet market? Suggestions for a specialized regulatory framework. Food Control 30, 705–713.
Li, Y., Zhang, H., Hu, J., Xue, F., Li, Y., Sun, C., 2012. A GC–EI-MS-MS method for simultaneous determination of seven adulterants in slimming functional foods. J. Chromatogr. Sci. 50, 928–933.
Marcheti, R.G.A., 2014. Evaluation of medicine counterfeiting in Brazil from forensic reports issued by the Brazilian Federal Police Department from 2006 to 2012 (Master dissertation). Universidade de Brasília, Brasília.
McCann, M., 2005. Dietary supplement labeling: cognitive biases, market manipulation & consumer choice. Am. J. Law Med. 31, 215–268.
Navarro, V.J., Seeff, L.B., 2013. Liver injury induced by herbal complementary and alternative medicine. Clin. Liver Dis. 17, 715–735.
Nogueira, F.R.S., Souza, A.A., Brito, A.F., 2013. Prevalence of the use and ergogenic resources effects by body builders in Brazilian academies: a systematic review. Rev. Bras. Ativ. Fís. Saúde 18, 16–30.
Oliver, A.S., León, M.T.M., Guerra-Hernández, E., 2011. Prevalence of protein supplement use at gyms. Nutr. Hosp. 26, 1168–1174.
Petroczi, A., Taylor, G., Naughton, D.P., 2011. Mission impossible? Regulatory and enforcement issues to ensure safety of dietary supplements. Food Chem. Toxicol. 49, 393–402.
Rebiere, H., Guinot, P., Civade, C., Bonnet, P.-A., Nicolas, A., 2012. Detection of hazardous weight-loss substances in adulterated slimming formulations using ultra-high-pressure liquid chromatography with diode-array detection. Food Addit. Cont. 29, 161–171.
Saeedi, P., Nasir, M.T.M., Hazizi, A.S., Vafa, M.R., Foroushani, A.R., 2013. Nutritional supplement use among fitness club participants in Tehran, Iran. Apetite 60, 20–26.
SVS (Brazilian Secretary of Health Surveillance), 1998. Portaria n° 32, de 13 de janeiro de 1998. – Aprova o regulamento técnico para suplementos vitamínicos e ou de minerais.
SVS (Brazilian Secretary of Health Surveillance), 1998b. Portaria n° 344, de 12 de maio de 1998 – Aprova o Regulamento Técnico sobre substâncias e medicamentos sujeitos a controle especial.
Sepkowitz, K.A., 2013. Energy drinks and caffeine-related adverse effects. J. Am. Med. Assoc. 309, 243–244.
Shahidi, N.T., 2001. A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. Clin. Ther. 23, 1355–1390.
Silva, A.A., Marins, J.C.B., 2013. Consumption and level of knowledge about nutritional ergogenic resources in athletes. Biosci. J. 29, 1038–1048.
Song, F., Monroe, D., El-Demerdash, A., Palmer, C., 2014. Screening for multiple weight loss and related drugs in dietary supplement materials by flow injection tandem mass spectrometry and their confirmation by liquid chromatography tandem mass spectrometry. J. Pharm. Biomed. Anal. 88, 136–143.
Tang, M.H.Y., Chen, S.P.L., Ng, S.W., Chan, A.Y.W., Mak, T.W.L., 2011. Case series on a diversity of illicit weight-reducing agents: from the well known to the unexpected. Br. J. Clin. Pharmacol. 71, 250–253.
Timcheh-Hariri, A., Balali-Mood, M., Aruan, E., Sadeghi, M., Riahi-Zanjani, B., 2012. Toxic hepatitis in a group of 20 male body-builders taking dietary supplements. Food Chem. Toxicol. 50, 3826–3832.
USA (United States of America), 1938. Federal food, drug, and cosmetic act. Public Law 75–717, 52. Stat. 1040 – 1059; June 25 1938. http://www.fda.gov/regulatoryinformation/legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm (last updated in December 5, 2011).
USA (United States of America), 1994. Dietary supplement health and education act of 1994. Public Law 103–417, 108. Stat. 4325 – 4335; October 25 1994.
USA (United States of America), 2011. FDA food safety modernization act. Public Law 111–353, 124. Stat. 3885 – 3973; January 4 2011.
USFDA (U. S. Food and Drug Administration), 1997. Food and drug administration modernization act. Public Law 105–115. Section 303.
USFDA (U. S. Food and Drug Administration), 2003. Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm053832.htm.
USFDA (U. S. Food and Drug Administration), 2007. Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Final Rule, 72 Federal Register 34752–34958, June 25, 2007.
USFDA (U. S. Food and Drug Administration), 2009. Guidance for Industry: Evidence-based Review System for the Scientific Evaluation of Health Claims – Final (U. S. Food and Drug Administration). 2011. Beware of Fraudulent 'Dietary Supplements'. http://www.fda.gov/food/guidanceregulation/ucm073332.htmUSFDA. http://www.fda.gov/forconsumers/consumerupdates/ucm246744.htm (Accessed 26.09.14.).
USFDA (U. S. Food and Drug Administration), 2011. Questions and Answers on Tainted Products Marketed as Dietary Supplements. Updated on March 23, 2011. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/ucm247094.htm (Accessed 29.09.14.).

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013

USFDA (U. S. Food and Drug Administration), 2013. OxyElite Pro Supplements Recalled. http://www.fda.gov/forconsumers/consumerupdates/ucm374742.htm (Accessed 29.09.14.).

USFDA (U. S. Food and Drug Administration), 2013b. FDA Uses New Authorities to Get OxyElite Pro off the Market. 2014 (Accessed on September 29). http://blogs.fda.gov/fdavoice/?s=dmaa.

USFDA (U. S. Food and Drug Administration), 2014. MedWatch Safety Alerts for Human Medical Products. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm (Accessed 30.12.14.).

USFDA (U. S. Food and Drug Administration), 2014b. Tainted Supplements CDER. http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?filter=&sortColumn=3a&sd=tainted_supplements_cder&displayAll=false&page=2 (Accessed 30.12.14.).

Van Poucke, C., Detavernier, C., Van Cauwenberghe, R., Van Peteghem, C., 2007. Determination of anabolic steroids in dietary supplements by liquid chromatography–tandem mass spectrometry. Anal. Chim. Acta 586, 35–42.

Vaysse, J., Balayssac, S., Gilard, V., Desoubdzanne, D., Malet-Martino, M., Martino, R., 2010. Analysis of adulterated herbal medicines and dietary supplements marketed for weight loss by DOSY ^{1}H-NMR. Food Addit. Cont. 27, 903–916.

Please cite this article in press as: Justa Neves, D.B.d., Caldas, E.D., Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market, Regulatory Toxicology and Pharmacology (2015), http://dx.doi.org/10.1016/j.yrtph.2015.06.013